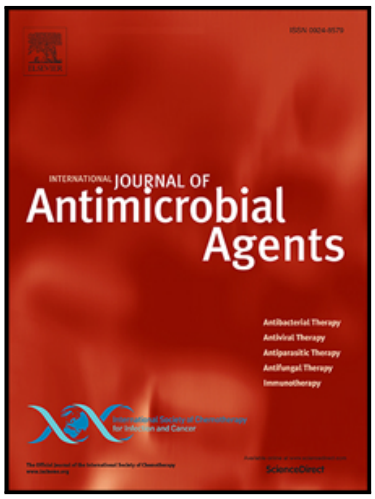

Predictors of outcome in patients with severe sepsis or septic shock due to extended-spectrum β-lactamase-producing Enterobacteriaceae

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HIGHLIGHTS

- Few data are reported in literature regarding sepsis or septic shock due to ESBL strains.
- The INCREMENT project is the largest international cohort study on ESBL infections.
- Septic shock due to ESBL strains is associated with high 30-day mortality rate.
- Escalation of antibiotic therapy is an important determinant of mortality.
- Carbapenems should be used only in strains with resistance to ß-lactam/ß-lactamase inhibitors

Predictors of outcome in patients with severe sepsis or septic shock due to extended-spectrum β-lactamase-producing Enterobacteriaceae

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ABSTRACT

Purpose: Few data are reported in literature regarding severe sepsis or septic shock due to extended-spectrum β-lactamases (ESBL)-producing Enterobacteriaceae (E). The aim of this study was to assess predictors of outcome in septic patients with bloodstream infection (BSI) caused by ESBL-E.

Methods: Patients with severe sepsis or septic shock and BSI due to ESBL-E were selected from the INCREMENT database. The primary endpoint of the study was the evaluation of predictors of outcome after 30 days from development of severe sepsis or septic shock due to ESBL-E infection. To perform analysis were created three cohorts: global, empirical-therapy and targeted-therapy cohorts.

Results: 367 septic patients were analyzed. Overall mortality was 43.9% at 30 days; *Escherichia coli* (62.4%) and *Klebsiella pneumoniae* (27.2%) were the most frequent isolates. β-lactam/β-lactamase inhibitor (BLBLI) combinations was the most empirically used drug (43.6%), followed by carbapenems (29.4%); empirical therapy resulted active *in vitro* in 249 (67.8%) patients, but an escalation of antibiotic therapy was reported in 287 (78.2%) patients. Cox regression analysis showed that age, Charlson Comorbidity Index, McCabe classification, Pitt bacteremia score, abdominal source of infection and escalation of antibiotic therapy were independently associated with 30-day mortality. No differences were reported about survival in patients treated with BLBLI combinations or carbapenems in empirical or definitive therapy.

Conclusions: BSI due to ESBL-E in patients who developed severe sepsis or septic shock was associated with high 30-day mortality; comorbidities, severity scores, source of infection and need of antibiotic therapy escalation were important determinants of unfavorable outcome.

Keywords: sepsis; septic shock; extended-spectrum ß-lactamases; carbapenems; ß-lactam/ß-lactamase inhibitors

INTRODUCTION

Bloodstream infections (BSI) caused by extended-spectrum β-lactamases (ESBL)-producing Enterobacteriaceae (E) are associated with high rates of treatment failure and increased mortality, especially when appropriate antimicrobial therapy is delayed [1-2-3-4-5]. On this basis, the choice of an early effective empirical antibiotic therapy in critically ill patients with sepsis and/or septic shock is crucial to reduce the high rates of complications and unfavourable outcome [5].

Previous publications resulting from the INCREMENT project [6-7-8-9-10] highlighted the necessity to identify peculiar clinical and therapeutic features of BSI due to ESBL strains. The role of carbapenems, considered the first choice for the treatment of severe infections caused by ESBL strains [11-12-13-14-15], was redefined also for the high incidence of carbapenem-resistant Enterobacteriaceae strains observed in the last few years [16]. On this basis, attention is now focused on promotion of carbapenem-sparing strategies and evaluation of efficacy of other drugs, like β-lactam/β-lactamase inhibitor combinations (BLBLI), that remain active against a considerable proportion of ESBL-E; however, the role of these drugs is controversial for the treatment of serious infections due to ESBL pathogens [17-18-19].

In this scenario, few data are reported in literature concerning sepsis or septic shock due to ESBL-E infections. Thus, it is important for physicians to recognize peculiar clinical characteristics of sepsis or septic shock due to ESBL-E infections, to promptly identify patients at high risk of unfavorable outcome. Based on this scenario, the aim of this additional study from the INCREMENT project was to assess the predictors of outcome in septic patients with severe sepsis or septic shock caused by ESBL-producing strains.

MATERIALS AND METHODS

Study Design and Patients

The INCREMENT project is a retrospective international cohort study including patients with clinically significant BSI due to ESBL- or carbapenemase-producing Enterobacteriaceae from January 2004 to December 2013. Characteristics of the INCREMENT study were previously explained [15-16-17-18-19]. This analysis was reported according to the STROBE recommendations [20].

Patients with severe sepsis or septic shock and clinically significant BSI due to ESBL-E were selected from the original database. Data from patients were collected up to 30 days after the diagnosis of BSI from charts; if needed, patients or relatives were contacted by phone.

The INCREMENT project was approved by the Spanish Agency of Medicines (AEMPS; code JRB-ANT-2012-01) and the Hospital Universitario Virgen Macarena Institutional Review Board (code 1921); the need to obtain written informed consent was waived. Approval was also gained at participating centers according to local requirements.

Variables, Microbiology and Definitions

Data collected from all patients included: demographics, acquisition of infection, comorbidities by calculation of Charlson comorbidity index, McCabe classification, Pitt bacteremia score, source of BSI according to clinical and microbiological data, antimicrobial therapy, *in* vitro susceptibility to empirical and targeted antibiotic regimens, length of stay after BSI, and mortality.

Enterobacteriaceae were identified using standard microbiological techniques in each participating center. ESBL-production was screened and confirmed according to CLSI

198 recommendations [21]; selected isolates from each center had been characterised by
199 polymerase chain reaction (PCR) and DNA sequencing using established methods [17].
200 Nosocomial acquisition was considered when symptoms of infection started >48 hours
201 after hospital admission or within 48 hours of hospital discharge, while we considered
202 healthcare acquisition if patients had attended haemodialysis or received intravenous
203 chemotherapy in the past 30 days, had been admitted to an acute-care hospital for at
204 least 2 days or had surgery in the past 90 days, or resided in a nursing home or long-
205 term care facility. Other infections were considered community-acquired.
206 For McCabe classification we used three categories: (1) non-fatal (mild and only a few
207 comorbidities), (2) ultimately fatal (risk of death within four years or multiple
208 comorbidities) and (3) rapidly fatal (risk of death during stay, intensive or terminal care
209 patients) underlying diseases.
210 Antimicrobial therapy administered before the susceptibility results were available was
211 considered empirical; therapy administered after microbiological report was considered
212 targeted/definitive.
213 Severe sepsis was defined as sepsis with sepsis-induced organ dysfunction or tissue
214 hypoperfusion (manifesting as hypotension, elevated lactate levels, or decreased urine
215 output); septic shock as severe sepsis plus persistently low blood pressure following the
216 administration of intravenous fluids [22].
217 Administered BLBLI were amoxicillin-clavulanate (AMC), piperacillin-tazobactam
218 (PTZ), or ampicillin-sulbactam (AMS), quinolones were ciprofloxacin or levofloxacin,
219 aminoglycosides were gentamicin or amikacin, while carbapenems included imipenem,
220 meropenem, and ertapenem. Therapy was considered as monotherapy if no other drugs
221 with intrinsic activity against gram-negative organisms were co-administered,
222 irrespective of isolate susceptibility.

Active empirical therapy was considered the appropriateness of antibiotic therapy for all patients with an etiologic diagnosis according to susceptibility test criteria. We rated an antimicrobial treatment as inadequate if 1 or more of the organisms present were known to have intrinsic resistance or were found to be resistant through susceptibility testing. Escalation of antibiotic therapy was defined as the switch to or addition of a drug class or classes with a broader spectrum or additional coverage after 48 hours from the initial antibiotic therapy.

Global, Empirical-therapy and Targeted-therapy cohorts

We constructed 3 non-mutually exclusive cohorts to analyze predictors of mortality, including also therapeutic variables. The global cohort (GC) included all patients analyzed but were explored only pre-treatment variables to identify factors associated with mortality, irrespective of antibiotic therapies. The impact of empirical therapy was investigated in the empirical-therapy cohort (ETC), which included the patients who received a monotherapy that began within the first 24 h after blood cultures were taken and continued for at least 48 h (except for patients who died in ≤48 h, who were included if they received at least 1 complete day of therapy). The impact of targeted therapy was investigated in the targeted-therapy cohort (TTC), which included the patients who received a monotherapy once the susceptibility profile was available; the targeted drug must have started in ≤5 days and been administered for at least 50% of the total duration of therapy (except for patients who died while on targeted therapy, who were included if they received at least 1 complete day of therapy).

Endpoints and Statistical Analysis

The primary endpoint of the study was the evaluation of predictors of outcome at 30 days after development of septic shock due to ESBL infection.

Separate analyses were performed for the three cohorts. To detect significant differences between groups, we used the chi-square test or Fisher exact test for categorical variables, and the 2-tailed *t* test or Mann-Whitney test for continuous variables, when appropriate. In univariate and multivariate analysis of survival, the Cox regression model was used to determine the effects of different variables on outcome at 30 days. The cumulative survival was evaluated using Kaplan-Meier product-limit estimators. The final multivariable Cox regression model was selected through forward stepwise regression based on Akaike Information Criterion.

Statistical significance was established at ≤ 0.05. All reported *P* values are 2-tailed. The results were obtained using the statistical software R (version 3.3.4; Vienna, Austria).

RESULTS

The INCREMENT database includes 1005 patients with BSI due to ESBL-E; out of these, 367 (36.5%) patients with severe sepsis or septic shock were analyzed. The number of cases per center in the global cohort ranged from 4 to 50 and wards of hospitalization at the time of ESBL-E isolation, in this study population, are reported in **Figure 1**.

Baseline characteristics and comparison about clinical features of survivors and non-survivors at 30 days are reported in **Table 1**. Overall, mortality at 30 days was observed in 161 (43.9%) patients. Comparison between the two patient groups showed that nosocomial acquisition of infection (64.5% Vs 50%, p=0.002), pneumonia (17.4% Vs 8.3%, p=0.012), admission in ICU (32.2% Vs 18.9%, p=0.004), a higher Charlson Comorbidity index (3 points Vs 2 points, p=0.005), a higher Pitt bacteremia score (4 points Vs 3 points, <0.001), need of NIV or MV (44% Vs 21.3%, p<0.001), and need of vasopressor agents (91.9% Vs 65%, p<0.001) were more frequently observed in non-survivors. Conversely, a urinary source of infection (44.7 Vs 24.8, p<0.001) was more frequently reported in survivors, compared to patients with poor outcome. Finally, time to appropriate antibiotic therapy (4 days Vs 3 days, p=0.01) was longer in non-survivors, compared to survivors.

Etiologies of infection are described in **Table 2**. Overall, *Escherichia coli* (62.4%) and *Klebsiella pneumoniae* (27.2%) were the most frequent isolates; *in vitro* resistance to antibiotics prescribed in empirical therapy, was observed in 4/5 (80%) strains of *Serratia marcescens*, 23/29 (79.3%) of *Enterobacter* spp, 123/229 (53.7%) of *Escherichia coli*, and 41/100 (41%) of *Klebsiella pneumoniae*. Comparison between

297 survivors and non-survivors showed a more frequent isolation of *Escherichia coli*
298 (67.5% Vs 55.9%, p=0.03) in survivors, while *Klebsiella pneumoniae* was more
299 frequently isolated in non-survivors (34.2% Vs 21.8%, p=0.012), compared to
300 survivors.

301 **Table 3** shows a comparison of antibiotics used in empirical and definitive regimens
302 among survivors and non-survivors. BLBLI was the most empirically used class
303 (43.6%), followed by carbapenems (29.4%), and cephalosporins (19.3%), while
304 carbapenems (56.4%), and BLBLI (10.4%) were more frequently used as definitive
305 therapy. A combination therapy was empirically used in 119 (32.4%) patients and in 93
306 (25.3%) patients as definitive regimen. Empirical antibiotics resulted *in vitro* active in
307 249 (67.8%) patients, and escalation of antibiotic therapy was used in 287 (78.2%)
308 patients. Comparison between non-survivors and survivors showed that a carbapenem in
309 definitive antibiotic regimen (42.9% Vs 67%, p<0.001) and a combination of antibiotics
310 as definitive therapy (16.7% Vs 32%, p<0.001) were more frequently used in the latter.
311 As reported in **Table 4**, univariate and multivariate Cox regression analysis about
312 predictors of outcome at 30 days in the GC showed that age (HR 1.11, CI 95% 1.02-
313 1.22, p=0.021), McCabe classification (HR 1.39, CI 95% 1.12-1.72, p=0.003), Pitt
314 bacteremia score (HR 1.14, CI 95% 1.09-1.19, p<0.001), and abdominal source of
315 infection (HR1.66, CI 95% 1.08-1.89, p=0.02) were independently associated with
316 death.
317 Based on inclusion criteria (see Methods section), 31 patients were excluded from ETC
318 and TTC to investigate the impact of therapy on 30-day mortality.
319 The **Table 5** shows that, at univariate and multivariate Cox regression analysis about
320 predictors of outcome at 30 days in 106 patients of the ETC, McCabe classification (HR
321 1.45, CI 95% 1.14-1.83, p=0.002), Pitt bacteremia score (HR 1.14, CI 95% 1.08-1.19,

p<0.001), and escalation of antibiotic therapy (HR 1.9, CI 95% 1.1-3.26, p=0.02) were independently associated with death.

Univariate and multivariate Cox regression analysis about predictors of outcome at 30 days in 230 patients of the TTC is reported in **Table 6**. Charlson Comorbidity Index (HR 1.20, CI 95% 1.11-1.30, p<0.001) and Pitt bacteremia score (HR 1.16, CI 95% 1.09-1.24, p<0.001) were associated with death, while was reported a protective role for quinolones in definitive therapy (HR 0.29, CI 95% 0.11-0.8, p=0.016).

Finally, Kaplan-Meier analysis of 30-day survival of patients in whom an escalation of antibiotic therapy was needed or not is reported in **Figure 2**.

DISCUSSION

This study highlights the high mortality associated with BSI due to ESBL-E at 30 days from diagnosis in patients who developed severe sepsis or septic shock; furthermore, some clinical characteristics like source of infection (specifically from urinary tract, abdominal or pneumonia), indicators of severity (like comorbidities and admission in ICU), need of respiratory support and/or vasopressor agents were important determinants of outcome in this setting.

However, Cox regression analysis identified age, McCabe classification, Charlson Comorbidity Index, Pitt bacteremia score, abdominal source of infection and escalation of antibiotic therapy (after microbiological report and/or worsening of clinical conditions) as factors independently associated with unfavourable outcome at 30 days. Finally, the use of a quinolone in definitive therapy was associated with 30-day survival.

As previously reported in literature, the severity of clinical conditions (expressed by age, McCabe classification, Charlson Comorbidity Index and Pitt bacteremia score) at time of BSI onset plays a central role in determining the decreased survival in patients with infections due to ESBL-E [23]; furthermore, the progression to sepsis and septic shock is the crucial mechanism associated with high rates of mortality observed in this setting of critically ill patients with BSI due to ESBL strains [24-25-26]. Progression to septic shock may explain the apparently low effectiveness also of an adequate initial

antibiotic therapy, since septic shock is associated with a lethal cascade of events that is unlikely to be interrupted even by an appropriate initial antimicrobial treatment. In addition, most of our patients were severely ill and would probably have been unable to survive their infections independently of the administration of an adequate initial antimicrobial treatment. Finally, the lack of homogeneity in management and treatment of septic patients could partly explain the high rates of mortality.

Of importance, the need of an antibiotic therapy escalation after microbiological report and/or worsening of clinical conditions was independently associated with unfavourable outcome at 30 days, confirming previous observations about an initial inadequate antimicrobial treatment as a major risk factor for mortality [27]. Moreover, severe infections could have an unfavorable outcome despite the administration of adequate antimicrobial treatment, due to the inability to raise plasma drug concentrations above the target MIC. This latter finding may be the cause of underexposure at the infection site, especially in critically ill patients, since septic patients usually require rapid and aggressive fluid resuscitation therapy with a subsequent increase in the extracellular fluid volume that could raise the volume of distribution of drugs [28]. On this basis, differences in rates of mortality could be related to the source of bacteremia. Several studies demonstrated a relationship between source of infection and clinical response [29], with bacteremia secondary to urinary tract infection usually associated with the lowest mortality rate [30]. In our population, as previously reported in literature [29], the abdominal source of infection was an independent determinant of unfavorable outcome considering the abovementioned observations.

An important finding of this analysis was the impact of empirical and definitive antibiotic regimens on 30-day outcome, especially for patients treated with carbapenem or BLBLI. The spread of carbapenemase-producing Enterobacteriaceae promoted

several studies about alternative therapies, like BLBLI. BLBLI has been evaluated for the treatment of these infections [18-31], but no definitive data were reported about the efficacy of BLBLI in the treatment of severe infections, when compared to carbapenems [14-32]. On this basis, the use of carbapenems should be optimized, recommending a role as empirical therapy only for patients who have high risk factors for colonization/infection, based also on geographical patterns of resistance about ESBL strains not susceptible to BLBLI, and on patients who are affected by non-urinary source of bacteremia [33]. In the remaining subjects, in whom clinical conditions or risk factors may not require immediate ESBL antimicrobial coverage, a guided therapy once culture results are obtained may be sufficient [34]. For these reasons, data from international trials will have to assess 30-day mortality associated with the use of BLBLI or carbapenems in the setting of ESBL infections [35]. Of interest, in our analysis quinolones resulted as protective in definitive therapy. The explanation is that, when active *in vitro*, quinolones were a reasonable choice in less critically-ill patients with urinary source of infection. The interpretation of this data is limited by the retrospective design of the study and only randomized trials could address a possible role of quinolones, also in severe infections. However, their use should be carefully evaluated considering the high rates of resistance reported, especially in area with an increased consumption of these antibiotics [36-37].

Of importance, the retrospective nature of the study is a limitation and all the considerations about the impact of empirical or targeted regimens on survival should be done with caution. Nevertheless, our series of septic shock associated with ESBL-E bacteremia is the largest ever reported in literature. Another study limitation is the lack of information of other variables that may influence the outcome, such as source control, circulatory management and PK/PD variables. Finally, no data were recorded

on long-term survival over 30 days; thus, we cannot provide more consistent information on the risk of recurrence of infection and emergence of resistant strains to antibiotic regimen used. However, in the database were applied very strict criteria for the cataloguing of antibiotic regimens and an important strength of this study is the multicenter and international participation to INCREMENT project, with collection of data from different countries.

CONCLUSIONS

In conclusion, these data point out the high 30-day mortality associated with BSI due to ESBL-E in patients who developed severe sepsis or septic shock, together with the importance of some clinical characteristics, like source of infection and indicators of severity, as determinants of patient's outcome in this setting, requiring an early escalation of antibiotic therapy. Moreover, these data confirm no differences in empirical and definitive antibiotic therapy of BSI, especially for BLBLI and carbapenems, in these critically ill patients. However, randomized clinical trials are needed to confirm these observations.

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All authors have access to the data and participated in the research and preparation of the manuscript.

DECLARATIONS

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Competing Interests: None to declare.

Ethical Approval: The INCREMENT project was approved by the Spanish Agency of Medicines (AEMPS; code JRB-ANT-2012-01) and the Hospital Universitario Virgen Macarena Institutional Review Board (code 1921).

APPENDIX

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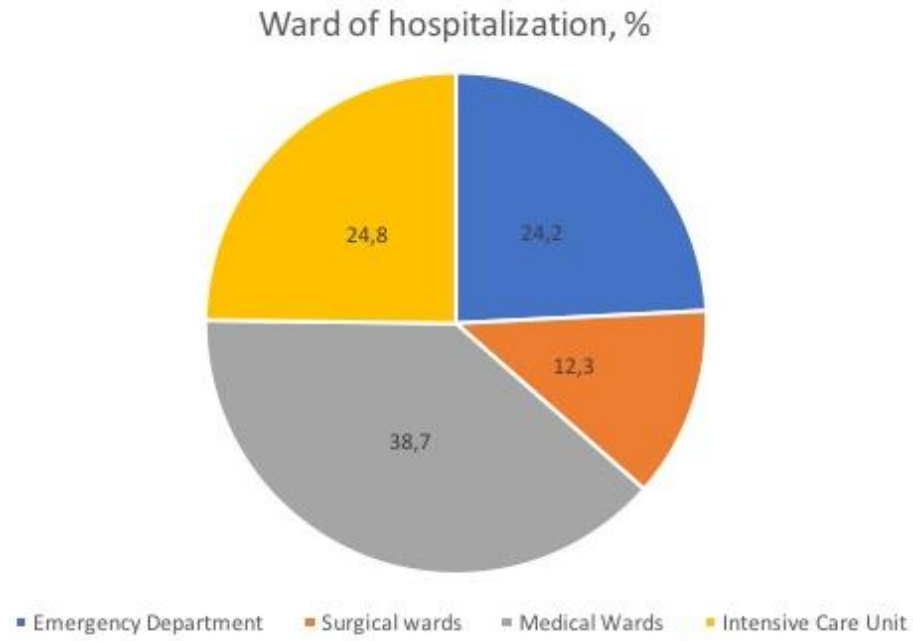
484 **Figure 1.** Wards of hospitalization at time of ESBL-E isolation

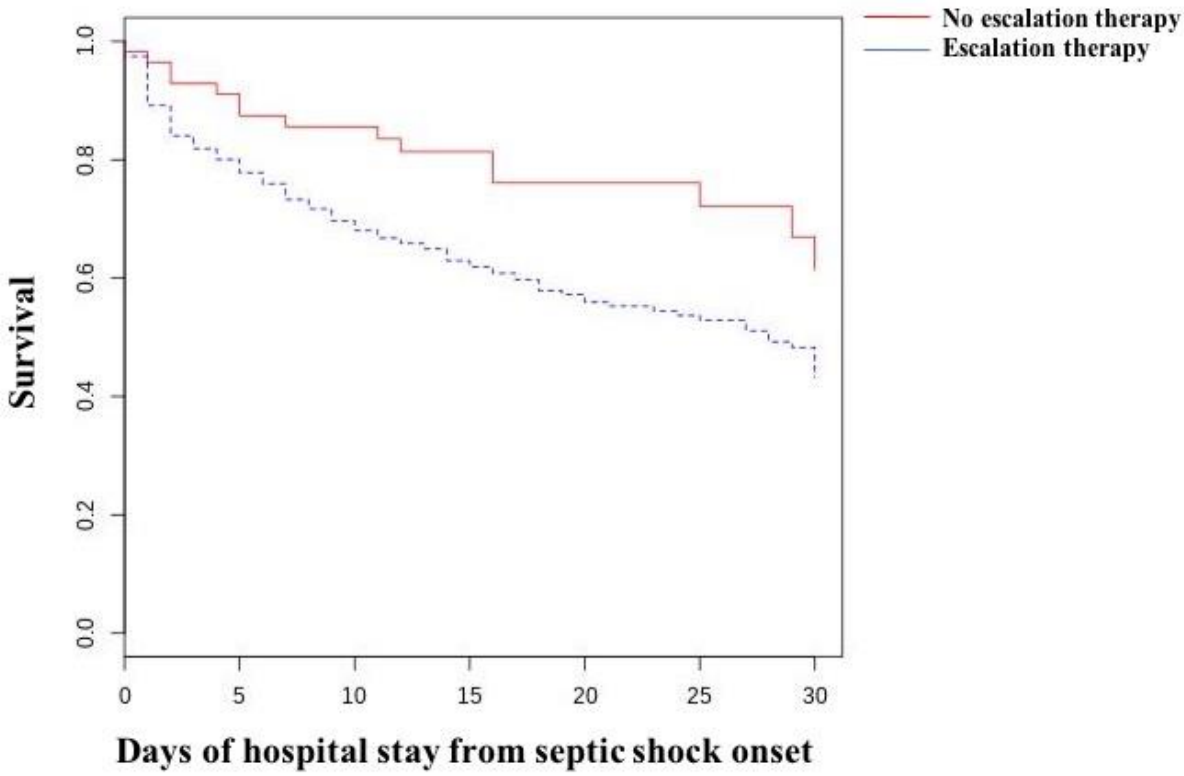


485

486 **Legend.** ESBL-E: extended-spectrum beta-lactamases-producing Enterobacteriaceae.

487

488 **Figure 2.** Kaplan-Meier curves about 30-day survival of patients in which
489 was needed or not an escalation of antibiotic therapy*



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491 *p<0.001

492

493 **Table 1.** Comparison about baseline characteristics and clinical features of
494 survivors and non-survivors at 30 days in the global cohort

Variables	All patients N=367 (%)	Survivors N=206 (%)	Non-Survivors N=161 (%)	*p*
Age, median (IQR)	69 (57-78)	68 (56-77)	70 (57-80)	0.30
Male sex	216 (58.9)	127 (61.7)	89 (55.3)	0.26
Acquisition of infection				
Community	46 (12.5)	30 (14.5)	16 (9.9)	0.26
Healthcare	106 (28.9)	70 (33.9)	36 (22.3)	**0.01**
Nosocomial	207 (56.4)	103 (50)	104 (64.5)	**0.002**
Source of infection				
Primary BSI	22 (6)	10 (4.9)	12 (7.5)	0.41
Urinary	132 (36)	92 (44.7)	40 (24.8)	**<0.001**
Biliary	36 (9.8)	23 (11.2)	13 (8.1)	0.42
SSTI	7 (1.9)	4 (1.9)	3 (1.9)	1.0
Abdominal	50 (13.6)	22 (10.7)	28 (17.4)	0.09
Pneumonia	45 (12.3)	17 (8.3)	28 (17.4)	**0.012**
Osteoarticular	2 (0.5)	2 (1)	0	0.59
CNS	1 (0.3)	0	1 (0.6)	0.90
Other	93 (25.3)	60 (29.1)	33 (20.4)	0.085
McCabe classification, nonfatal	145 (39.5)	97 (47)	48 (29.8)	**<0.001**
Charlson Comorbidity Index, median (IQR)	3 (1-5)	2 (0-4)	3 (2-8)	**0.005**
Pitt bacteremia score, median (IQR)	3 (2-5)	3 (1-4)	4 (2-7)	**<0.001**
Comorbidities				
Diabetes	124 (33.8)	60 (29.1)	64 (39.7)	**0.027**
COPD	77 (21)	37 (17.9)	40 (24.8)	0.09
Myocardial infarct	47 (12.8)	20 (9.7)	27 (16.7)	0.12
Congestive heart failure	70 (19.1)	31 (15)	39 (24.2)	**0.027**
Peripheral arterial disease	40 (10.9)	16 (7.8)	24 (14.9)	**0.046**
Dementia	41 (11.2)	22 (10.7)	19 (11.8)	0.83
Immunological disease	16 (4.4)	9 (4.3)	7 (4.3)	1.0
Ulcerative disease	23 (6.3)	12 (5.8)	11 (11.1)	0.81
Liver disease	58 (15.8)	31 (15)	27 (16.7)	0.68
Kidney disease	84 (22.9)	41 (19.9)	43 (26.7)	0.12
Cancer	148 (40.3)	88 (42.7)	60 (37.2)	0.43
Neurological disease	77 (21)	36 (17.4)	41 (25.4)	0.08
AIDS	8 (2.2)	6 (2.9)	2 (1.2)	0.47
ICU admission	91 (24.8)	39 (18.9)	52 (32.2)	**0.004**
Need of NIV or MV	115 (31.3)	44 (21.3)	71 (44)	**<0.001**
Need of vasopressor agents	282 (76.8)	134 (65)	148 (91.9)	**<0.001**

Time to appropriate antibiotic therapy, days, median (IQR)	3 (1-5)	3 (1-4)	4 (2-5)	**0.01**

Legend. IQR: inter-quartile range; BSI: bloodstream infection; SSTI: skin and soft tissue infection; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; AIDS: acquired immune deficiency syndrome; ICU: intensive care unit; NIV: non-invasive mechanical ventilation; MV: mechanical ventilation.

Table 2. Etiology of infection among survivors and non-survivors at 30 days and rate of resistance to empirical therapy

Pathogens	**Survivors** N=206 (%)	**Non-Survivors** N=161 (%)	***p***	**Resistance to empirical therapy** N° resistant isolates/ total isolates (%)
Escherichia coli	139 (67.5)	90 (55.9)	**0.03**	123/229 (53.7)
Klebsiella pneumoniae	45 (21.8)	55 (34.2)	**0.012**	41/100 (41)
Enterobacter spp	17 (8.3)	12 (7.5)	0.93	23/29 (79.3)
Serratia marcescens	3 (1.5)	2 (1.2)	1.0	4/5 (80)
Proteus spp	0	2 (1.2)	0.37	0
Citrobacter spp	1 (0.5)	0	1.0	0
Morganella morganii	1 (0.5)	0	1.0	0

Table 3. Comparison between antibiotics administered in empirical and definitive therapy to survivors and non-survivors at 30 days in the global cohort

Antibiotics	**Empirical therapy**			**Definitive therapy**		
	Survivors N=206 (%)	**Non-Survivors N=161 (%)**	***p***	**Survivors N=206 (%)**	**Non-Survivors N=161 (%)**	***p***
Cephalosporin	43 (20.9)	28 (17.4)	0.48	3 (1.5)	1 (0.6)	0.80
BLBLI	94 (45.6)	66 (41)	0.43	27 (13.1)	11 (6.8)	0.07

Aminoglycosides	22 (10.7)	21 (13)	0.59	16 (7.8)	8 (5)	0.39
Quinolones	30 (14.6)	25 (15.5)	0.91	14 (6.8)	6 (3.7)	0.29
TMP/SMX	1 (0.5)	0	1.0	8 (3.9)	4 (2.5)	0.65
Fosfomycin	2 (1)	0	0.59	0	0	-
Tetracycline	2 (1)	2 (1.2)	1.0	0	0	-
Monobactams	1 (0.5)	1 (0.6)	1.0	0	0	-
Colistin	1 (0.5)	1 (0.6)	1.0	3 (1.5)	1 (0.6)	0.79
Carbapenem	61 (29.6)	47 (29.2)	0.44	138 (67)	69 (42.9)	**<0.001**
Tigecycline	0	0	-	6 (2.9)	2 (1.2)	0.47
Chloramphenicol	0	0	-	1 (0.5)	0	1.0
Combination therapy	150 (72.8)	111 (68.9)	0.54	88 (42.7)	49 (30.4)	**0.001**
Median length of therapy (IQR)	3 (1-4)	2 (1-4)	0.1	11 (5-14)	7 (3-10)	**<0.001**
Active empirical therapy	143 (69.4)	106 (65.8)	0.54			
Escalation of antibiotic therapy	154 (74.7)	133 (82.6)	0.09			

Legend. BLBLI: ß-lactam/ß-lactamase inhibitor; TMP/SMX: Trimethoprim/sulfamethoxazole: IQR: inter-quartile range.

Note. BLBLI: amoxicillin/clavulanate or ampicillin/sulbactam or piperacillin-tazobactam

Quinolones: ciprofloxacin or levofloxacin

Aminoglycosides: gentamicin or amikacin

Carbapenem: meropenem or imipenem or ertapenem

Table 4. Univariate and Multivariate Cox regression analysis about predictors of outcome at 30 days in 367 patients of the global cohort

VARIABLES	**UNIVARIATE**			**MULTIVARIATE**		
	HR	**95%CI**	***p***	**HR**	**95%CI**	***p***
Age	1.1	1.01-1.21	0.031	1.11	1.02-1.22	0.021
Male sex	0.84	0.62-1.15	0.284			
Acquisition of infection						
Healthcare	0.95	0.53-1.71	0.863			
Nosocomial	1.38	0.81-2.34	0.233			

Source of infection						
Primary BSI	1.08	0.6-1.94	0.807			
Urinary	0.59	0.41-0.84	0.003			
Biliary	0.81	0.46-1.44	0.478			
SSTI	0.82	0.26-2.57	0.735			
Abdominal	1.46	0.97-2.19	0.07	1.66	1.08-1.89	0.02
Pneumonia	0.45	1.04-2.36	0.3			
ICU admission	1.4	1.01-1.95	0.047			
Charlson Comorbidity Index	1.05	0.99-1.11	0.083			
McCabe classification	1.54	1.25-1.89	<0.001	1.39	1.12-1.72	0.003
Pitt bacteremia score	1.14	1.09-1.19	<0.001	1.14	1.09-1.19	<0.001
Comorbidities						
Diabetes	1.42	1.03-1.95	0.033			
COPD	1.28	0.89-1.84	0.175			
Myocardial infarct	1.29	0.85-1.96	0.238			
Congestive heart failure	1.28	0.87-1.84	0.19			
Peripheral arterial disease	1.41	0.91-2.18	0.12			
Dementia	1.08	0.67-1.75	0.752			
Immunological disease	0.82	0.39-1.76	0.617			
Ulcerative disease	1.08	0.58-1.99	0.816			
Liver disease	1.11	0.73-1.68	0.629			
Kidney disease	1.31	0.92-1.87	0.132			
Cancer	0.85	0.62-1.18	0.334			

AIDS	0.43	0.11-1.72	0.232			
Need of NIV or MV	1.93	1.4-2.64	<0.001			
Need of vasopressor agents	1.37	1.01-2.08	0.044			

Legend. HR: hazard ratio; CI: confidence interval; BSI: bloodstream infection; SSTI: skin and soft tissue infection; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; AIDS: acquired immune deficiency syndrome; NIV: non-invasive mechanical ventilation; MV: mechanical ventilation.

Table 5. Univariate and Multivariate Cox regression analysis about predictors of outcome at 30 days in 106 patients of the empirical-therapy cohort

VARIABLES	**UNIVARIATE**			**MULTIVARIATE**		
	HR	**CI 95%**	***p***	**HR**	**CI 95%**	***p***
Age	1.09	0.99-1.19	0.075			
Male sex	0.82	0.59-1.13	0.226			
Acquisition of infection						
Healthcare	0.95	0.52-1.74	0.861			
Nosocomial	1.36	0.79-2.35	0.270			
Source of infection						
Primary BSI	1.19	0.66-2.15	0.562			
Urinary	0.56	0.39-0.82	0.003			
Biliary	0.87	0.49-1.54	0.639			
SSTI	0.85	0.27-2.68	0.786			
Abdominal	1.42	0.93-2.17	0.104			
Pneumonia	1.79	1.18-2.72	0.006			

ICU admission	1.58	1.12-2.23	0.009			
Charlson Comorbidity Index	1.06	0.99-1.12	0.069			
McCabe classification	1.55	1.25-1.93	<0.001	1.45	1.14-1.83	0.002
Pitt bacteremia score	1.16	1.11-1.22	<0.001	1.14	1.08-1.19	<0.001
Comorbidities						
Diabetes	1.37	0.98-1.92	0.062			
COPD	1.45	1.01-2.1	0.047			
Myocardial infarct	1.43	0.92-2.21	0.111			
Congestive heart failure	1.43	0.98-2.09	0.06			
Peripheral arterial disease	1.25	0.77-2.03	0.357			
Dementia	0.98	0.58-1.65	0.934			
Immunological disease	0.79	0.35-1.80	0.58			
Ulcerative disease	1.09	0.57-2.07	0.797			
Liver disease	1.12	0.73-1.73	0.593			
Kidney disease	1.43	0.99-2.05	0.056			
Cancer	0.91	0.65-1.27	0.578			
AIDS	0.44	0.11-1.78	0.249			
Need of NIV or MV	1.96	1.41-2.72	<0.001			
Need of vasopressor agents	1.69	1.14-2.49	0.008			
Cephalosporin	0.87	0.57-1.31	0.494			
BLBLI	0.95	0.69-1.32	0.763			
Aminoglycosides	1.06	0.67-1.68	0.808			
Quinolones	1.12	0.73-1.73	0.595			

Tetracycline	1.34	0.33-5.44	0.677			
Carbapenem	1.02	0.72-1.44	0.914			
Combination therapy	0.78	0.65-1.11	0.12			
Escalation of antibiotic therapy	1.92	1.12-3.28	0.017	1.9	1.1-3.26	0.02
Time to appropriate antibiotic therapy	1.2	0.87-2.34	0.25			

Legend. HR: hazard ratio; CI: confidence interval; BSI: bloodstream infection; SSTI: skin and soft tissue infection; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; AIDS: acquired immune deficiency syndrome; NIV: non-invasive mechanical ventilation; MV: mechanical ventilation.

Table 6. Univariate and Multivariate Cox regression analysis about predictors of outcome at 30 days in 230 patients of the targeted-therapy cohort

VARIABLES	**UNIVARIATE**			**MULTIVARIATE**		
	HR	**CI 95%**	***p***	**HR**	**CI 95%**	***p***
Age	1.1	1.01-1.21	0.031			
Male sex	1.19	0.62-1.15	0.284			
Acquisition of infection						
Healthcare	0.95	0.53-1.72	0.863			
Nosocomial	1.38	0.81-2.34	0.233			
Source of infection						
Primary BSI	1.73	0.79-3.76	0.169			
Urinary	0.68	0.41-1.13	0.137			
Biliary	1.53	0.79-2.99	0.208			

SSTI	1.71	0.54-5.41	0.365			
Abdominal	0.92	0.44-1.92	0.829			
Pneumonia	1.52	0.87-2.68	0.144			
ICU admission	1.4	1.01-1.95	0.047			
Charlson Comorbidity Index	1.05	0.99-1.11	0.083	1.20	1.11-1.30	<0.001
McCabe classification	1.54	1.25-1.89	<0.001			
Pitt bacteremia score	1.14	1.09-1.19	<0.001	1.16	1.09-1.24	<0.001
Comorbidities						
Diabetes	1.42	1.03-1.95	0.033			
COPD	1.29	0.89-1.84	0.175			
Myocardial infarct	1.29	0.85-1.96	0.238			
Congestive heart failure	1.28	0.89-1.84	0.19			
Peripheral arterial disease	1.41	0.91-2.18	0.12			
Dementia	1.08	0.67-1.75	0.752			
Immunological disease	0.66	0.21-2.09	0.475			
Ulcerative disease	1.08	0.58-1.99	0.816			
Liver disease	1.11	0.73-1.68	0.629			
Kidney disease	1.31	0.92-1.87	0.132			
Cancer	0.85	0.62-1.18	0.334			
AIDS	0.43	0.11-1.72	0.232			
Need of NIV or MV	1.88	1.18-3.0	0.008			
Need of vasopressor agents	1.32	0.79-2.18	0.287			
Cephalosporin	1.46	0.1-4.91	0.708			

BLBLI	1.64	0.33-1.13	0.114			
Aminoglycosides	0.59	0.29-1.20	0.142			
Quinolones	0.54	0.24-1.22	0.141	0.29	0.11-0.8	0.016
TMP/SMX	1.01	0.32-3.19	0.992			
Colistin	0.5	0.07-3.61	0.493			
Carbapenem	0.96	0.54-1.71	0.883			
Tigecycline	0.3	0.04-2.2	0.239			
Combination therapy	0.59	0.39-1.22	0.24			

Legend. HR: hazard ratio; CI: confidence interval; BSI: bloodstream infection; SSTI: skin and soft tissue infection; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; AIDS: acquired immune deficiency syndrome; NIV: non-invasive mechanical ventilation; MV: mechanical ventilation.

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